IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF TEXAS
MARSHALL DIVISION

ERFINDERGEMEINSCHAFT UROPEP GbR, Plaintiff, v. ELI LILLY AND COMPANY, and BROOKSHIRE BROTHERS, INC., Defendants.	)	CASE No. 2:15-cv-01202-WCB

PLAINTIFF UROPEP'S COMBINED OPPOSITION TO DEFENDANT'S MOTIONS FOR SUMMARY JUDGMENT ON INFRINGEMENT AND INDEFINITENESS

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

Statutes

INTRODUCTION

The standard *in vitro* measure of potency, IC_{50}, has been around since the 1970s, Lilly admits. Using IC_{50} ratios to define selectivity of PDE inhibition is definite enough to use in patents, Lilly has also admitted. And 146 United States patents use "IC50" in patent claims, including a Lilly patent on using PDE5 inhibitors. Whether the PDE material comes from a recombinant source instead of live tissue does not materially affect selectivity determinations, Lilly's expert has sworn under oath.

With these admissions, how can Lilly present its (untimely) motion for summary judgment of indefiniteness on the theory that it is "impossible" to determine selectivity with reasonable certainty? How can Lilly argue, with literally no evidence, that using recombinant PDE isozymes makes any difference – and thus UroPep's reliance on the Cialis label to show infringement is inadmissible?

Lilly can say these things because it has litigated this case on a "good for me but not for thee" theory of patent law. Lilly's candid views are not in its briefs, but rather in Lilly's representations to the PTO and the public. Lilly's US Patent No. 6,451,807 defines selectivity by reference to IC_{50} ratios, tells us that *in vitro* testing under a variety of conditions can be used to determine such IC_{50} data, and even uses IC_{50} ratios in its claims. To invalidate a Pfizer patent that threatened Lilly, Lilly's own employee expert Dr. Florio testified in direct opposition to its new "recombinant is different" argument. Lilly has chosen not to mention these admissions to the Court, leaving it to the adversary system to bring to the surface evidence that directly contradicts Lilly's arguments.

After all of that, Lilly asks the Court to deliberately mis-read the claims and prosecution history to require selectivity as to PDE6-11. These isozymes are unmentioned in the specification and not the subject of the prior art Heiker compounds that gave rise to the disclaimer the Court

based its construction on. Most importantly, requiring selectivity as to PDE6 would exclude every single example compound of the specification from coverage, a construction which is "rarely, if ever, correct." *Clare v. Chrysler Grp. LLC*, 819 F.3d 1323, 1331 (Fed. Cir. 2016) (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1583 (Fed. Cir. 1996)). The correct measure of selectivity for PDE5 is against PDE1-4 – the exact one Lilly's Dr. Florio relied on when Lilly successfully convinced the USPTO to invalidate Pfizer's claims to using a "selective cGMP PDE_V inhibitor" to treat erectile dysfunction.

As a last-ditch effort to get out of this Court and this case, Lilly asks for yet another construction based on the PDEs that a skilled worker would "likely" (Lilly's word) find doing fractionation tests on human prostate tissue. Lilly's expert did not say such a result was "likely," but instead that it "might … if … could potentially" happen. What Lilly also does not tell the Court is that its own published research shows that tadalafil is over 40x more selective for PDE5 than the PDE11 variant found in the prostate – again the exact opposite of what it represents to the Court in its brief.

The '124 patent asserted claims are definite, and the use of Cialis to treat BPH definitely infringes those claims. Based on Lilly's conduct and the arguments it has presented to this Court in these summary judgment briefs, a jury should be permitted to decide whether that infringement is willful. Lilly's reliance on the adversary system to check non-disclosure, exaggerations, and misstatements justifies UroPep's allegation of willful infringement.

LEGAL STANDARD

"Summary judgment is granted 'if the movant shows that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law.'" *Raytheon Co. v. Indigo Sys. Corp.*, 688 F.3d 1311, 1314-15 (Fed. Cir. 2012) (quoting Fed. R. Civ. P. 56(a)). When reviewing a summary judgment ruling, the court "'views all evidence in the light most

favorable to the non-moving party and draws all reasonable inferences in that party's favor.'" *Id.* at 1315 (quoting *Griffin v. United Parcel Serv., Inc.*, 661 F.3d 216, 221 (5th Cir. 2011)) (applying Fifth Circuit law and reversing grant of summary judgment where the dispute presented fact issues). "Viewing the evidence in the light most favorable to" the nonmoving party, "a genuine issue of material fact [] precludes summary judgment." *Optical Disc Corp. v. Del Mar Avionics*, 208 F.3d 1324, 1339 (Fed. Cir. 2000) (reversing grant of summary judgment).

Claims satisfy the definiteness requirement if, when "viewed in light of the specification and prosecution history, [they] inform those skilled in the art about the scope of the invention with reasonable certainty." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2129 (2014). "The ultimate conclusion that a claim is indefinite under 35 U.S.C. § 112, ¶ 2 is a legal conclusion." *Cox Commc'ns, Inc. v. Sprint Commc'n Co. LP*, 838 F.3d 1224, 1228 (Fed. Cir. 2016). However, "[a]ny fact critical to a holding on indefiniteness . . . must be proven by the challenger by clear and convincing evidence." *Id.* (citations omitted; ellipses in original).

"A determination of infringement . . . is a question of fact." *Golden Blount, Inc. v. Robert H. Peterson Co.*, 365 F.3d 1054, 1058 (Fed. Cir. 2004). "Any doubt as to the existence of any issue of material fact requires denial of the motion." *Omega Eng'g, Inc., v. Raytek Corp.*, 334 F.3d 1314, 1320, 1329 (Fed. Cir. 2003) (reversing summary judgment of non-infringement "[b]ecause a reasonable jury might reach different conclusions when faced with this evidence"). Similarly, "[w]illfulness of behavior is a classical jury question of intent. When trial is had to a jury, the issue should be decided by the jury." *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1341 (Fed. Cir. 2016) (quoting *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1250 (Fed. Cir. 1989)). Where the jury finds willfulness, the ultimate question of whether to enhance damages is

committed to the court's discretion. *See id.* at 1342 (deferring to the court's discretionary decision to enhance damages by 50%).

ARGUMENT

I. LILLY FORFEITED ITS INDEFINITENESS CHALLENGE AND THE CLAIMS ARE DEFINITE, IN ANY EVENT

Lilly has violated the Docket Control Order in this case by presenting indefiniteness arguments outside of the *Markman* process and cannot show good cause for failure to obey the DCO. Even granting Lilly the immunity to scheduling orders it believes itself to have, the claims of the '124 patent are definite under the Court's construction. Lilly has assembled a laundry list of assay conditions for *in vitro* testing and remarked that there will be variations in IC_{50} values depending on those conditions. That is why UroPep's Dr. Bell says it is best not to directly compare *absolute* values of IC_{50} (measured in units of micro- or nanomolar) from one lab or article to another. But selectivity is a unitless ratio of two IC_{50} measurements, and the variance is attenuated by looking at this unitless ratio. Ex. 1-B, Bell Validity Rpt. ¶¶ 60-61.

There will always be experimental error in any measurement such as this, which is not a computer program, calculation of the slope of a line, or any other mathematical endeavor for which there is a precise answer. Data in the prior art should be considered with that experimental error in mind. But whether or not more measurements are needed to reduce the experimental error depends on the compound and whether it is close to the borderline or not. That is why there is no dispute that tadalafil meets the Court's 20x selectivity requirement when PDE1-4 are compared to PDE5. The data we have, even with generous experimental error, leaves no doubt.

Lilly knows all of this, and has admitted that selectivity using IC_{50} ratios provides reasonable certainty in proceedings before the PTO. First, when it obtained its '807 patent, Lilly used IC_{50} ratios to define selectivity (there between PDE1, PDE5 and PDE6), provided limited if

any guidance as to all the conditions Lilly today says are critical, and then used IC_{50} ratios to define the scope of the claims. Second, when it faced Pfizer's '012 patent, Lilly presented the PTO with the Florio Declaration, in which Lilly felt free to "modify" the methods disclosed in the Pfizer '012 patent in order to determine the selectivity of two prior art compounds using IC_{50} ratios. Lilly assured the PTO that its modifications did not matter.

What Lilly has done here is, at most, generated a fact issue as to whether zaprinast meets the Court's test. But, as Dr. Bell explains, when the best data is reviewed with the lowest margin of error, zaprinast is clearly a selective PDE5 inhibitor. Experimental error can be reduced through additional experiments. If zaprinast were the accused product and Lilly was not flaunting a product label that admitted infringement, maybe UroPep would need to do more experiments to minimize this error. Such additional experimentation is routine. There is no problem determining, with reasonable certainty, whether a PDE5 inhibitor is selective under the Court's definition.

A. Lilly Violated The Docket Control Order By Presenting Indefiniteness Outside Of The *Markman* Process And Supporting Its Indefiniteness Brief With An Untimely Expert Opinion

Lilly never raised indefiniteness of this term at the claim construction phase of this case, forfeiting its right to do so now under the Docket Control Order. Lilly also failed to include most of the evidence they rely on to support their indefiniteness arguments in their opening expert reports, as required by the DCO.

Every version of the DCO stated, in a bold and underlined section that

> **Indefiniteness**: In lieu of early motions for summary judgment, the parties are directed to include any arguments related to the issue of indefiniteness in their Markman briefing, subject to the local rules' normal page limits.

See, e.g., Dkt. 65 at 4 (emphasis in original). This language in the DCO has been entered and re-entered ten times – both before and after the claim construction ruling – without Lilly ever once asking the Court for relief from the above-quoted provision.

Lilly did not present indefiniteness at the *Markman* stage as to the "inhibitor of phosphodiesterase (PDE) V" claim term. Dkt. 84 at 3 (Joint Claim Construction and Prehearing Statement showing Lilly contended two other terms were indefinite but not this one). Lilly's excuse for waiting until now will doubtless place blame on the Court for its construction requiring a 20x selectivity for PDE5. But, as the Court observed in its claim construction order, UroPep consistently urged a claim construction that included a selectivity requirement. Dkt. 149 at 24. Lilly did not respond that such a requirement (even without the more specific 20x standard) would render the claim indefinite. The DCO prohibits this sort of indefiniteness opportunism. *Cf. Droplets, Inc. v. Overstock.com, Inc.*, No. 2:11-CV-401-JRG-RSP, 2015 WL 11120799, at *2 (E.D. Tex. Jan. 9, 2015) (striking expert reports on indefiniteness where not raised in *Markman* proceedings because indefiniteness is an issue of law for the Court at claim construction).

As is now a pattern, Lilly will ask for freedom from the DCO. Yet Lilly has failed to identify the required good cause for its deviation from the scheduling order. Dkt. 181 at 10 (Unclean Hands Ruling) ("The party seeking to modify a scheduling order has the burden to show good cause"). And even assuming the Court's construction provides justification to raise an indefiniteness challenge immediately after that construction was given, that cannot explain why Lilly failed to seek relief from the DCO and address this issue to the Court for three months.

Lilly further violated the DCO by failing to disclose most of the evidence they cite to support their indefiniteness arguments in their opening expert reports. The DCO has consistently

set forth two expert report deadlines. *See, e.g.*, Dkt. 151, 8th Amended DCO. The first deadline was for "Disclosures for Expert Witnesses by the Party with the Burden of Proof." The second is for "Disclosures for Rebuttal Expert Report Witnesses." *Id.* Lilly has the burden on indefiniteness, so any expert opinions relating to indefiniteness needed to be disclosed in Lilly's opening reports.

Lilly's table on zaprinast and much of Lilly's opinion testimony and evidentiary support for its entire indefiniteness brief come from Dr. Rotella's Responsive Report, served on January 14, 2017.[1] *See* Dkt. 173, Lilly Indef. Br. 4, 5, 9 (repeatedly citing Rotella Responsive Report). *See also id*. at 7-8 (reproducing, without attribution, the bulk of a chart on zaprinast from the Rotella Responsive Report, see Ex. 2 ¶ 25). This expert report from Dr. Rotella was allegedly in response to UroPep's infringement allegations. Dr. Rotella did not offer any opinion regarding indefiniteness in his opening expert report on validity. Ex. 3, Rotella Expert Rpt. ¶ 1. Lilly not only went around the DCO in presenting indefiniteness outside of claim construction, it went around the DCO by presenting new arguments and evidence on validity in its responsive expert reports on infringement. Lilly is stuck with its opening reports and the evidence cited therein, which is Dr. Beavo's report and his very thin allegations. Ex. 4, Beavo First Rpt. A party cannot use responsive expert reports to shore up deficiencies on issues where it bears the burden of proof. Lilly has no good cause for failing to disclose these arguments and evidence in its opening expert reports on validity, including virtually all of the arguments on zaprinast.

In all events, Lilly's late-raised indefiniteness arguments are futile. The experimental conditions Lilly now says are so rigid it has previously told the PTO and the public are, in fact,

[1] Dr. Beavo did serve a validity report and had some opinions on indefiniteness, but without any of the supporting detail Lilly is relying on for its motion. In all events Lilly violated the DCO by presenting this outside of the claim construction process as earlier noted.

quite flexible. The Court should credit what Lilly said when it was getting its own patents, not what it is saying to try to escape UroPep's. The IC_{50} measurements and selectivity ratios generated from them are subject to experimental error – that does not make them indefinite. Lilly has conflated the certainty of such experimental error with an absence of reasonable certainty.

B. Lilly Conflates The Certainty Of Experimental Error With An Absence Of Reasonable Certainty

Measurement error happens every time a scientific experiment is performed, whether it uses a ruler or an IC_{50} assay. Such measurement error is commonplace with IC_{50} assays and it has nothing to do with the "assay conditions" Lilly lists. Dkt. 173, Lilly Indef. Br. at 9, ¶ 22. That is why Lilly's own Daugan paper, using a single set of assay conditions, reports a measurement error of ± 25% in the calculation of an IC_{50}.

Table 6. PDE5 Activity and Selectivity of **12a** on PDE Isoforms

	IC_{50} (μM)[d]						IC_{50} ratio	IC_{50} ratio
compd	PDE1[a]	PDE2[b]	PDE3[a]	PDE4[b]	PDE5[a]	PDE6[c]	PDE1/5	PDE6/5
12a	>10	>10	>10	>10	0.005	5.1	>2000	1000
sildenafil **1**	1.1	>10	9.2	7.8	0.006	0.074	180	12

[a] Bovine aorta PDE. [b] Human recombinant PDE. [c] Bovine retina PDE. [d] IC_{50} values were reproducible to ±25%.

Ex. 5, Daugan 2003 Part 2 at 4538. Sometimes, scientific studies do not even report measurement error because the data is not meant to be interpreted quantitatively, but rather qualitatively. A good example of that is the Terrett 1996 article, which shows results of only two measurements and does not report measurement error. Ex. 6, Terrett 1996 at 1820. Beyond measurement error, using PDEs obtained from multiple tissue sources introduces additional experimental error in the form of impurities in the PDE sample. Ex. 1-B, Bell Validity Rpt. ¶¶ 28, 38. Controlling this sort of error is why the '124 patent refers to obtaining the tissue from a single source. Ex. 7, '124 patent col. 7, ll. 41-42 ("Fresh tissue obtained during an operation.").

In this case, experimental error does not pose a problem in determining whether tadalafil (compound 12a above) meets the Court's construction, because its selectivity ratios are so high

that there is no question that the use of tadalafil infringes. To the extent a particular compound is borderline (as Lilly contends is the issue with zaprinast), the person of skill can reduce both types of error – measurement error by taking more measurements and tissue-source error by using one source like the '124 patent says to.

When it comes to zaprinast, instead of intelligently discussing scientific measurements and experimental error, Lilly obsesses with the point estimates of selectivity ratios it calculates (sometimes making basic arithmetic errors in the process – errors that always seem to benefit Lilly's case). Lilly then ignores both reported error (if there is any) and the experimental error introduced by using multiple living tissue sources. Take Coste 1995, which Lilly thinks supports its view that zaprinast does not meet the Court's construction. The measurement error in the PDE5 IC_{50} mean is a whopping 50%. Ex. 8, Coste 1995 at 1579 (0.2 ± 0.1 μM). The error in the PDE1 IC_{50} mean is 20%. *Id.* (3 ± 0.6 μM). The actual PDE1/PDE5 ratio could thus be anywhere between 8 and 36 when looking at the lower bound of the PDE5 IC_{50} and the upper bound of the PDE1 IC_{50}. Ex. 1-B, Bell Validity Rpt. ¶ 80. Or take Lilly's own publication, Daugan 2003, where the 25% measurement error in IC_{50} makes the selectivity ratio for zaprinast range possibly up to and over 20x.[2] Lilly never discusses measurement error.

Lilly cites the Terrett 1996 IC_{50} data on zaprinast, reported with no measurement error (there are only two measurements) and using tissue from multiple sources. Lilly thinks this is some sort of "gotcha" because Dr. Bell is a co-author and if you divide the IC_{50} values for PDE1 and PDE5 you get a number less than 20. One difference between scientists and lawyers is that the former does not engage in such a crude calculation without acknowledging the concept of

[2] In Daugan, zaprinast has a reported PDE5 IC_{50} of 0.2 ± 25% so it could be as low as 0.15. For PDE1 it is 2.6 ± 25% so it could be as high as 3.25. The ratio could thus be as high as 3.25/0.15 = 21.7 just taking into account measurement error alone. *See* Ex. 9, Daugan 2003 Part 1 at 4528.

error bars. The Terrett 1996 report was not a study designed to determine the selectivity of zaprinast to the level of specificity of the Court's construction but is instead a qualitative comparison showing the improved selectivity of sildenafil. Far from "disregarding" his own article, Dkt. 173, Lilly Indef. Br. 18-19, Dr. Bell addressed this very issue in his report. Ex. 1-B, Bell Validity Rpt. ¶ 38. The skilled person does not cherry pick IC_{50} values from papers without due regard for experimental error, divide them together to obtain point estimates with no error bars and then declare defeat (or a lack of reasonable certainty) because they are different. The skilled person reads papers and understands the experimental error associated with the methods at issue, and can find the best data that minimizes that error. As Dr. Bell explains, that turns out to be the Takase and Saeki papers, which demonstrate a selectivity ratio for zaprinast well in excess of 20x with very low measurement error[3] using the same living tissue source.[4] *See* Ex. 1-B, Bell Validity Rpt. ¶¶ 37-38; 80-81.

Lilly's zaprinast table is also riddled with error and overstatements. Many of the articles provide no measurement error, meaning they are not intended to be used to calculate a selectivity

[3] Compare Coste's error of 50% in PDE5 $IC_{50,}$ Ex. 8, Coste 1995 at 1579, and Saeki's error in the same calculation of less than 20%, Ex. 10, Saeki 1995 at 827 (0.51 ± 0.1 μM). For PDE1, Coste's error is 20% (3 ± 0.6 μM), but Saeki's for the same value is **4%** (49.4 ± 2.5 μM). Saeki is just the better study.

[4] This just goes to show how easy it is to minimize measurement error. Coste used 3 measurements and got an error of 50%. Saeki used 4 measurements and got an error of less than 20%. What error is acceptable depends on what one is trying to show. If the goal is to show that tadalafil is 20x more selective for PDE5 than PDE1, an error of 50% is just fine, because tadalafil is (according to Daugan) more than 2000x more selective for PDE5 over PDE1. Fifty percent error does not come even close to the 20x threshold of the Court's construction. Lilly has shown that for zaprinast, a closer case, we need to look to better data, like that from Saeki. So what?

ratio with good precision.[5] Instead, these articles provide only a qualitative measure. For others, Lilly has miscalculated the selectivity reported. For example the Souness article, by the creators of zaprinast, reports that zaprinast (M&B 22,948) is 60-fold more selective for PDE5 (cGMP specific) than PDE1 (Ca^{2+} PDE).

metabolism. M&B 22,948 is a selective inhibitor of cyclic GMP hydrolysis and has been an important tool in establishing a causal role for cyclic GMP in a number of biological events. This azapurinone inhibits both cGMP PDE and Ca^{2+} PDE (see Table 2, Lugnier *et al.*, 1986), exhibiting approximately 60 fold greater potency against the former activity. In

Ex. 11, Souness at 731. How Lilly got to its calculation on Souness (arriving at a lower than 20x selectivity), is a mystery, given that Lilly did not include the article as an exhibit to its briefs (or any of the other articles from its table) and its expert provides no explanation of how he got Lilly's number in his inadmissible hearsay expert report. Ex. 2, Unsworn Rotella Resp. Rpt.; *Duarte v. City of Lewisville*, 136 F. Supp. 3d 752, 773 (E.D. Tex. 2015) (striking unsworn expert reports submitted for purposes of summary judgment proceedings).[6] And Dr. Rotella's unsworn expert report did not even provide a full citation of Souness (Ex. 2, Unsworn Rotella Resp. Rpt. ¶ 25), and did not attach it as an exhibit. UroPep should not have to do the hard work of locating and reading the articles that Lilly's expert is relying on to figure out that the art says the opposite of what Lilly is saying.

[5] See Addendum 1 at the end of this brief. Those articles not reporting measurement error are highlighted in orange. The measurement error from the four articles that remain are shown.

[6] All of Lilly's expert reports have not been sworn and are inadmissible hearsay. The Court can, and should, deny summary judgment to Lilly on this basis. *Provident Life & Accident Ins. Co. v. Goel*, 274 F.3d 984, 1000 (5th Cir. 2001) ("Unsworn expert reports ... do not qualify as affidavits or otherwise admissible evidence for [the] purpose of Rule 56, and may be disregarded by the court when ruling on a motion for summary judgment.") (quotation and footnote citation omitted). Additionally, as discussed above, Dr. Rotella's indefiniteness opinions are untimely and should therefore be excluded.

Lilly even goes so far as to accuse its own researchers of reporting two different selectivity ratios for zaprinast in consecutive articles from the same volume of the same journal. *Compare* Lilly Indefiniteness Br. at ¶ 18 (citing Ex. 9, Daugan 2003 Part 1 as reporting 13-fold selectivity) with ¶ 20 ("In another paper by the same authors on the same subject matter published at the same time in the same journal, zaprinast was reported to have about 6.67 fold selectivity to PDE5 versus PDE1"). No. The table that Lilly put in its own brief to support the 6.67 fold selectivity number actually shows zaprinast with an IC_{50} for PDE5 of 0.2µM and an IC_{50} for PDE1 of 2.6µM. Again, ignoring measurement error and doing Lilly's arithmetic for them, 2.6/0.2 is 13. Ex. 9, Daugan 2003 Part 1 at 4528 Table 5.

Table 5. PDE5 Activity and Selectivity of Hydantoins on PDE Isoforms

	IC_{50} (μM)[c]	IC_{50} (μM)			
compd	PDE5[a]	PDE1[a]	PDE2[b]	PDE3[a]	PDE4[b]
lead-**2**	0.3	2	nd[d]	>10	>10
Zaprinast-**3**	0.2	2.6	>10	>10	>10
trans-**6e**	0.005	>10	>10	>10	>10
cis-**6e**	0.008	>10	>10	>10	>10
cis-**6m**	0.004	>10	>10	>10	>10
cis-**6n**	0.007	>10	>10	>10	>10
sildenafil	0.006	1.1	>10	9.2	7.8

[a] Bovine aorta PDE. [b] Human recombinant PDE. [c] IC_{50} values were reproducible to ±25%. [d] Not determined.

At the end, for all Lilly makes of the variable data it derives (and frequently mis-reports) for zaprinast, it has not provided any evidence that assay conditions or anything else produce the same variance for data on tadalafil, sildenafil, or any other much-studied PDE5 inhibitor. Nor does the existence of the variability mean that it is the assay conditions that were responsible for any difference. Indeed, when one looks at the best studies, those that actually attempt to measure selectivity[7] and control for what can be controlled, zaprinast clearly meets the Court's definition. Ex. 1-B, Bell Validity Rpt. ¶¶ 80-82.

[7] Lilly's table is also a Frankenstein's monster of biology research that merely attempts to show qualitatively what PDEs are present and play a role in what tissue (like the Truss articles) and medicinal chemistry references that actually purport to be discussing the selectivity (qualitatively or quantitatively) of PDE inhibitor compounds (as the Daugan, Takase, Terrett, and Saeki articles do).

Far from being "a perfect example of the indefiniteness of the '124 patent claims," Dkt. 173, Lilly Indef. Br. 17, zaprinast is the only example Lilly can find of even a whisper of a need for additional data in determining whether it meets the Court's construction. If defendants could invalidate a patent as indefinite every time there was an apparent dispute about whether a single accused instrumentality infringed, then the denial of summary judgment of infringement would dictate a finding of indefiniteness. *Cf. Nautilus*, 134 S. Ct. at 2129 ("The definiteness requirement, so understood, mandates clarity, while recognizing that absolute precision is unattainable.").

Lilly's burden here is especially significant because it has to show that a measurement it used for itself in its own patent is not good enough for UroPep. Lilly has to show a lack of reasonable certainty not just as applied to the extant data on zaprinast, but in general and with respect to data that could be generated by the person of skill. Lilly has not come close to establishing these facts with clear and convincing evidence.

This data on zaprinast existed when Lilly applied for the '807 patent in 1999. But Lilly did not have any trouble defining its invention by reference to use of selective PDE5 inhibitors bounded by IC_{50} ratios. Lilly's '807 patent uses IC_{50} ratios to define selectivity and allows for the use of varying assay conditions to measure it.

C. Lilly's '807 Patent Uses IC_{50} Ratios To Define Selectivity And Endorses A Wide Variety Of Source Material And Assay Conditions To Measure It

Lilly's '807 Patent sought to leverage the discovery that tadalafil was selective for PDE5 over PDE6 and PDE1 by claiming:

> A method of treating sexual dysfunction in an individual suffering from a retinal disease comprising administering an oral dosage form comprising about 1 to about 20 mg of a **selective PDE5 inhibitor** having

> (i) at least a 100-fold differential in IC_{50} values for the inhibition of PDE5 versus PDE6,
>
> (ii) at least 1000-fold differential in IC_{50} values for the inhibition of PDE5 versus PDElc,
>
> (iii) an IC_{50} less than 10 nM, and
>
> (iv) a sufficient bioavailability to be effective in about 1 to about 20 mg unit oral dosages.

Ex. 12, '807 patent col. 20, ll. 45-56 (emphasis added). The specification defines "selective PDE5 inhibitor" by reference to the IC_{50} ratios outlined in the body of the claim above.[8] Ex. 10, '807 patent, col. 4, ll. 19-33.

Lilly's indefiniteness brief tells this Court that "IC50 values and selectivity ratios can vary widely depending upon the experimental conditions used." Dkt. 173, Lilly Indef. Br. 13. Lilly identifies those conditions in a bulleted list, which break down into two groups, the source of the PDE material, and the conditions of the IC_{50} measurement:

[8] The Court may remember the '807 patent because UroPep has cited it before. The sentence following the definition of "selective PDE5 inhibitor" says "Selective PDE5 inhibitors vary significantly in chemical structure, and their use in the present invention is not dependent on chemical structure, but rather on the selectivity and potency parameters disclosed herein." Ex. 12, '807 patent, col. 4, ll. 29-33. That is the opposite of Lilly's written description argument on which the Court denied summary judgment. Lilly is both constructively (it is their patent) and actually (UroPep has cited it before) on notice of what this patent says on the subject of measuring selectivity. And yet Lilly fails to bring this art, of its own making, to the Court's attention.

22. The '124 Patent does not specify any of the following experimental variables that would be part of a general fractionation test to determine IC50 values and selectivity ratios:

Source material
- Type of tissue
- Source of tissue (human or animal)

Assay conditions
- The concentration and purity of the enzyme
- The properties of the assay buffer
- The substrate concentration
- The presence of divalent cations such a Ca, Mg, and Mn
- The presence of salts such as NaCl and KCl
- The presence of EDTA (a chelating agent)
- The presence of reducing agents such as DTT
- The presence of a carrier such as BSA
- The presence of detergents such as Triton
- The presence of a solubilizer such as DMSO
- The type of buffer and pH.

Beavo First Report at ¶ 35.

Id. at 9 (citing Ex. 4, Beavo First Rpt. ¶ 35).

As to the source material, Lilly's '807 patent commits the sin (according to Lilly, today) of mixing and matching living-sourced and recombinant-sourced PDE. Ex. 12, col. 11, ll.36-37, col. 12, l. 43 (detailing human recombinant PDE5 preparation and PDE6 preparation obtained from bovine retinas).[9] As to assay conditions, like the '124 patent the '807 patent provides a set of conditions for the IC_{50} measurement – by citing a prior art reference. In the '124 patent that is the Galvan paper and the Nicholson paper (Ex. 7, '124 patent col. 7, ll. 38-39) and in the '807 patent it is the Cheng paper from 1973 (Ex. 12, '807 patent, col. 4, ll. 3-6) and the Wells paper from 1975 (*id.* col. 14, ll. 56-57). But Lilly's patent is quick to inform the Patent Office and the public that the assay conditions are not a straightjacket in a section entitled "IC_{50} Value Determinations:"

> "The concentration of inhibitor is always much greater than the concentration of enzyme"

[9] As discussed below in connection with Lilly's non-infringement argument, there is no problem with this at all because, according to Lilly's own expert, using recombinant versus living sourced material does not matter.

> "A suitable range of inhibitor concentrations is chosen …. Typically, inhibitor concentrations ranged from 10 nM to 10 µM"
>
> *[UroPep ed. note: this is a concentration range that varies by a factor of one thousand from one end to the other]*
>
> "The concentrations of enzyme and substrate are chosen such that less than 20% of the substrate is consumed in the absence of inhibitor …."
>
> *[UroPep ed. note: no guidance as to what that is so it must be that the skilled person can determine it]*

Ex. 12, '807 patent col. 14, ll. 12-39. And those are literally all the conditions given by Lilly's not indefinite '807 patent – there is no requirement about "[t]he presence of a solubilizer such as BSA" or "[t]he type of buffer and pH." What follows in the '807 specification are descriptions of specific experiments in accordance with Wells, but the '807 patent does not say those are the only conditions that can be used. Just like the '124 patent does not say one must follow the exact conditions of Galvan or Nicholson, which provide all the missing detail Lilly is demanding:

Assay of phosphodiesterase activity

Phosphodiesterase activity was assayed by the radiochemical procedure described by Arch & Newsholme (1976). The incubation medium consisted of 50 mM Tris/HCl, 6 mM $MgCl_2$, 2.5 mM dithiothreitol, 0.05 mg ml^{-1} 5′nucleotidase, 0.23 mg ml^{-1} bovine serum albumin and the relevant concentrations of [^{3}H]-adenosine 3′:5′-cyclic monophosphate ([^{3}H]-cyclic AMP), [^{3}H]-guanosine 3′:5′-cyclic monophosphate ([^{3}H]-cyclic GMP), cyclic GMP, calmodulin and Ca^{2+}; pH 7.5. The reaction was initiated by the addition of 30 µl of enzyme preparation and tubes were incubated for 10 min at 30°C. The reaction was terminated by the addition of 1.2 ml of an anion-exchange resin slurry (BIO-RAD AG 1 × 8, 200–400 mesh). The tubes were centrifuged (200 *g* for 15 min) and a portion (0.25 ml) of supernatant was added to 5 ml of scintillation fluid (Aqualuma). Radioactivity was measured in a liquid scintillation counter.

The total radioactivity in the substrate at zero time was measured in the supernatant when all the substrate had been converted into product by addition of commercial phosphodiesterase (10 µg). Assays were conducted in the linear reaction range, where less than 50% of the initial substrate was hydrolysed. All assays were repeated at least three times.

Assay of Phosphodiesterase. Phosphodiesterase activity was measured as previously described by Bauer and Schwabe (1980) in a reaction mixture containing 40 mM Tris (pH 8.0), 5 mM $MgCl_2$ and 0.1 mg/ml bovine serum albumin. ^{3}H-labeled cyclic nucleotides were added with 50,000 cpm per assay (200 µl), the concentration of the unlabelled cyclic nucleotides being 0.5 µM. Drugs were added in 2 µl DMSO solution resulting in a 1% DMSO concentration in the assay. Incubation was started by addition of enzyme (5–20 µl) and was performed at 37°C. The reaction was stopped by adding 50 µl 0.2 N HCl and cooling on ice for 10 min. 50 µl of snake venom (Ophiophagus hannah; 1 mg/ml in 0.2 N Tris pH 8.0; Bauer and Schwabe 1980) were added, the resulting mixture was again incubated at 37°C and was stopped on ice after 10 min. 200 µl of the assay volume were added to small columns (Econo-column, Biorad) containing 1 ml QAE-Sephadex. 2 ml of 30 mM ammonium formate (pH 6.0) were added to the column and the eluate was collected directly in scintillation vials which were counted for radioactivity after addition of 10 ml scintillation fluid.

Ex. 13, Galvan 1990 at 222 (right);[10] Ex. 14, Nicholson 1989 at 890 (left). Of course, these assay conditions can have some effect on the absolute IC_{50}, but that says nothing about whether the relative IC_{50} and thus the selectivity ratios are substantially different. Ex. 1-B, Bell Validity Rpt. ¶¶ 58-61.

Lilly's '807 patent is not the only one to rely on an IC50 measurement to define the scope of the claims. One-hundred and forty-six US patents use the term "IC50" in their claims.[11] While space does not permit delving into the 145 of these that are not the '807 patent, the Court can certainly consider the possibility that given what Lilly and its brethren in the pharmaceutical industry have done with patents, Lilly is just asking for a "a restricted railroad ticket, good for this day and train only." *Smith v. Allwright*, 321 U.S. 649, 669 (1944) (Roberts, J., dissenting)

If assay conditions are so important to understand selectivity data, why does the Cialis label contain selectivity data and no assay conditions? Ex. 16, Cialis Label at 12.1. Why did the '807 patent not tell the world that only the method of Wells could be used to determine selectivity for purposes of its claims? Rather than focus on what it has said before regarding using selectivity to define the scope of patent claims, Lilly focuses on Federal Circuit cases dealing with altogether different problems.

D. Lilly's Cases Address Altogether Different Contexts, Not Experimental Error – Precise Mathematical Calculations, The Uniqueness Of Each Human Being's Urinary EPO, A Proposed Use-

[10] Lilly mischaracterizes Galvan in order to criticize it as "unhelpful," Lilly Indef. Br. 12. Lilly says Galvan shows two specific PDEs in a single peak. It does not. Ex. 1-B, Bell Validity Rpt. ¶ 31.

[11] See Ex. 15, USPTO Patent Full-Text And Image Database; search for "ACLM/IC50" http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO2&Sect2=HITOFF&u=%2Fnetahtml%2FPTO%2Fsearch-adv.htm&r=0&f=S&l=50&d=PTXT&RS=ACLM%2FIC50&Refine=Refine+Search&Query=ACLM%2FIC50 (last visited January 31, 2017).

Based Construction Of A Composition Claim, And The Application Of Different Software To Produce Different Outputs

Lilly's cases involve a lack of reasonable certainty where there were multiple analytically distinct approaches to determining whether the claim was met, not where there was one experiment and the art tolerated a variety of conditions for performing it, as Lilly's '807 patent admits regarding IC_{50} measurement.

Dow Chemical Co. v. Nova Chemicals Corp. (Canada), 803 F.3d 620, 633 (Fed. Cir. 2015) does not involve biochemistry, but rather determining the slope of a curve – an endeavor of math. *Id.* The patentee admitted there were four different mathematic methods of calculating the slope of the relevant curve and that "these four methods may produce different results." *Id.* UroPep does not admit that there are four different measurements of IC_{50} (there is only one – the concentration at which 50% inhibition is achieved) or selectivity (a simple ratio of IC_{50} values) or that different assay conditions can produce meaningfully different results for selectivity ratios once measurement and experimental error is taken into account. The math of *Dow Chemical* does not tolerate experimental error, so if four different calculations of a slope produce four different answers that is a problem. But Federal Circuit precedent permits patentees to define their claims to capture the variation of experimental error. *Cf. BJ Servs. Co. v. Halliburton Energy Servs., Inc.*, 338 F.3d 1368, 1372 (Fed. Cir. 2003) (patentee successfully argued that "the term 'about' is intended to encompass the range of experimental error that occurs in any measurement").[12] Lilly has not even bothered to calculate the error of all the data it cites on

[12] Of course the claims of the '124 patent also do not use the term "about," and neither does Lilly's '807 patent. But the selectivity requirement comes from the Court's construction, and UroPep believes it is not meant to imply a certainty the art does not permit (*i.e.* that selectivity be shown to 20.0000x). The fact that the selectivity requirement permits the variability associated with experimental error does not render the term indefinite. *See Freeny v. Apple Inc.*, No. 2:13-cv-00361-WCB, 2014 WL 4294505, at *5 (E.D. Tex. Aug. 28, 2014) (collecting cases where courts have found somewhat "imprecise claim language not indefinite").

zaprinast, which at best would show that more measurements needed to be taken to nail down a more precise number. Lilly also has not shown that there is any problem of high variance with the selectivity data on tadalafil, sildenafil, or any other much-studied PDE5 inhibitor.

Four different sets of IC_{50} assay conditions, or four different sets of living tissues from which to obtain PDEs do not produce different "answers" but instead point estimates with associated experimental error. If the error is too large, then it might require additional measurements for a jury to find that the Court's construction is met, but that does not mean the claim term is indefinite. This is not the mathematical determination of the slope of a curve, it is the scientific measurement of the concentration of inhibitor necessary to achieve a 50% effect.

In *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1322 (Fed. Cir. 2003), the claim was found indefinite because it defined itself as having a glycosylation that differed from human urinary erythropoietin.[13] The problem with the claim in *Amgen* was that it required determining whether the accused product was different from a comparator different by Another's design – human urinary EPO (every person is different in this regard). *Id* at 1341. The comparator in the claim in *Amgen* was thus a "moving target." *Id.* But the comparator in the '124 patent claims stands still. It is the number 20 in the Court's construction of the '124 patent claims and in Lilly's '807 patent that number is 100 and 1000.

Geneva Pharmaceuticals, Inc. v. GlaxoSmithKline PLC, 349 F.3d 1373, 1384 (Fed. Cir. 2003) is even further afield, as it is not even an indefiniteness case, but a case rejecting a claim construction that made infringement of a composition depend on how it was being used. In *Geneva*, the Federal Circuit rejected the patentee's proposed construction of "synergistically effective amount" that required the amount to be synergistic for every combination of "antibiotic,

[13] Glycosylation is the addition of "carbohydrate side chains to amino acid residues." *Id.* at 1340.

bacteria, and disease." *Id.* The court reasoned that such a construction would render the claim indefinite because under it a given accused composition would infringe, or not, depending on how it was being used. *Id.*; *accord IPXL Holdings, L.L.C. v. Amazon.com, Inc.*, 430 F.3d 1377, 1384 (Fed. Cir. 2005) (apparatus claims with method steps are invalid as indefinite). The '124 patent claims are not apparatus claims, they are methods, and *Geneva* has nothing to do with this case.

Finally, *Butamax Advanced Biofuels LLC v. Gevo, Inc.*, 117 F. Supp. 3d 632, 639 (D. Del. 2015), *reconsideration denied*, No. 12-1036-SLR, 2015 WL 4919975 (D. Del. Aug. 18, 2015), provides an excellent bookend to *Dow Chemical*. *Butamax* involves not the scientific method and experimental error, but the different outputs that multiple different commercial computer software programs could produce with the same input. *Id.* at 640 ("different sequence alignment programs can provide different alignments for two given sequences, affecting the calculation of % identity"). Because the specification said "any commercially available or independently developed software" could be used, the claim was indefinite – just like the claim in *Dow Chemical* was indefinite because there were four mathematical approaches to determining the slope of a curve. *Id.* at 641. There is no experimental error in the single number output of the computer program in *Butamax*. Lilly has strayed very far from the art represented by the '124 patent and its own '807 patent. None of its cases involve a known calculation in the art that is known to have variation arising from experimental error associated with it.

This case is more like *Ethicon Endo-Surgery, Inc. v. Covidien, Inc.*, 796 F.3d 1312, 1316 (Fed. Cir. 2015). There, the Federal Circuit reversed the district court's finding that claims directed to surgical shears requiring an "average" clamping pressure in a given range were indefinite. The district court held the claims indefinite because the patent did not specify the

"method of measurement, the location of measurement, and the type and amount of tissue used for the measurement." *Id.* at 1317. The court disagreed, concluding that those of skill in the art would understand that determining the "average clamping pressure as recited by the claims can be accomplished by measuring the clamping force applied by the clamping arm at the midpoint of the clamping surface area," because the force along the clamping arm was generally linear and the midpoint "approximated the average of two force measurements taken at proximal and distal locations." *Id.* at 1318-19. The court was not concerned that plaintiff had "used four different methods to measure clamping force, and that each of these methods appeared to yield different force measurements," *id.* at 1319, because "each of these methods was designed to provide the same clamping force measurement," *id.* at 1320, and "while the actual tested clamping force measurements may have varied slightly between these methods, this was simply due to natural variances in real-world testing conditions." *Id.* Further, it noted, plaintiff's "witness explained that [i]f you took [results from] all [four of] the methods again and again and again, the average of all those [measurements] should be quite similar to each other." *Id.* (citations and quotations omitted; alterations in original). Thus, where a person of skill would know how to optimize experimental conditions – measuring at the midpoint in *Ethicon*; controlling for tissue source in our case – and could reduce measurement errors by taking multiple measurements – a technique relevant to the art in *Ethicon* and to this case – the claims are definite.

***

Lilly argues that no one could write a patent claim that defined selectivity based on IC_{50} ratios because this experimental error renders it so inherently uncertain. But Lilly already wrote such a claim for itself, in the '807 patent, and the error it complains about can be reduced using known techniques like taking more measurements. One-hundred forty-five other US patents use

"IC_{50}" in their claims. In this case, Lilly never once provides any evidence connecting experimental error in IC_{50} measurements to the varying assay conditions it has talked at length about. (Remember Daugan 2003 has measurement error of 25% while using the same assay conditions).

Lilly's non-infringement argument is no different in kind and no better in quality. Lilly argues that UroPep cannot rely on Lilly's own selectivity tests that used recombinant PDEs and Lilly should get summary judgment of non-infringement. The mere fact that Lilly says this when its own employee expert testified exactly to the contrary to the PTO both ends this argument on the merits and provides a basis for UroPep's continuing allegation of willful infringement. Lilly's other non-infringement arguments rest on two invalid glosses on the Court's claim construction, and as to the second of them Lilly has misrepresented the data on PDEs in the prostate to support a non-infringement defense – data that Lilly itself generated and published.

II. THE COURT SHOULD DENY LILLY'S MOTION FOR SUMMARY JUDGMENT OF NON-INFRINGEMENT AND GRANT PARTIAL SUMMARY JUDGMENT OF INFRINGEMENT TO UROPEP

The '124 patent refers to "five different sPDEs." Ex. 7, '124 patent, col. 1, l. 60. It later says that "A substance is considered an inhibitor of an sPDE if the concentration thereof which is necessary for inhibiting 50% of the substrate hydrolysis (IC_{50}) is at least 20 times lower in the respective peak fraction containing the specific phosphodiesterase than in other peak fractions." *Id.* col. 8, ll. 5-9. The Court relied on these statements in rendering its construction, and Lilly abuses both to attempt to earn itself a non-infringement judgment.

A. Lilly's Own Expert Says Using Recombinant Versus Living Tissue Derived PDEs Makes No Material Difference In An IC_{50} Test

First, Lilly says that its own Cialis label is not competent evidence of infringement because the selectivity tests therein "all used recombinant DNA enzymes,"[14] Lilly Noninfringement Br. 12, and not PDEs obtained from fractionation of living tissue. Lilly goes on to tell the Court that "the test using recombinant enzymes may be much more sensitive than a peak-fraction test such that the scope of which compounds are included or excluded from the claims changes if one changes the test." Dkt. 174, Lilly Noninfringement Br. 13. Notably, no Lilly expert supports that proposition, which is a *non sequitur* anyway – the solution to less sensitive tests is to take more measurements and reduce measurement error. And Lilly's argument will be news to its own employee and expert Dr. Florio, who helped Lilly invalidate Pfizer's '012 patent by doing tests, on recombinant material, to show that a prior art compound was a selective PDE5 inhibitor. It did not bother Dr. Florio that he was using recombinant material whereas the Pfizer patent used living tissue. No, he swore:

> "[I]n my experience, use of recombinant human PDE5 rather than PDE5 derived from human corpus cavernosum should not materially affect the IC_{50} results."

Ex. 18, Florio Declaration ¶ 10. Dr. Florio's declaration shows that tests on recombinant PDEs are the same as tests on PDEs obtained from living tissue and over half of Lilly's summary judgment motion of non-infringement is junked by its own prior admission. The Cialis label and the tests disclosed therein establish that tadalafil is more than 20x more selective for sPDEs 1-4

[14] This is another good example of how Lilly constantly over- and mis-states the evidence. The testing on tadalafil it references used PDE6 obtained from human retinal tissue through fractionation. Ex. 17, Nonclinical Pharmacology Rpt., at 8-9. Granted, the other PDEs were obtained from recombinant sources, proving the source does not matter.

than sPDE5. Lilly is making an argument for non- infringement, supported by none of its current experts and at odds with what its employee testified to at the PTO.

Lilly then proffers two glosses on the Court's claim construction. The first is based on Lilly's view that the discussion of selectivity in the '061 patent file history somehow referred to PDEs that were not present in the prior art Heiker reference, were not discussed in the specification, and were either unknown at the priority date (PDE11) or thought to be impossible to select PDE5 over (PDE6). The Court should reaffirm that the selectivity measurement is made against PDE1-4 for the reasons UroPep has urged in its motion for summary judgment of infringement.

B. The Appropriate Measure Of Selectivity Is Against The sPDEs Mentioned In The '124 Patent – PDE1-4; Not Against Irrelevant And As-Yet Undiscovered PDEs

UroPep has already presented argument on why the appropriate measure of selectivity is against PDE1-4 in its motion for summary judgment of infringement. Dkt. 176, UroPep Mtn. for Confirmation of Claim Construction Order and Partial Summary Judgment of Infringement, 9-13. Without burdening the Court with redundant argument, to summarize:

a. The '124 patent only discusses PDE1-5, calls them by the special term "sPDE" and then defines selectivity by reference to the other sPDEs.

b. The prosecution of the '061 patent that the Court relied on involved distinguishing the prior art compounds of Heiker, which were non-selective as to PDE2 and PDE1. Ex. 1-B, Bell Validity Rpt. ¶ 22.

c. The prior art stated that all PDE5 inhibitors also inhibited PDE6, meaning it would be impossible to sensibly discuss a PDE5 selective inhibitor as one that was selective over PDE6. Ex. 1-B, Bell Validity Rpt. ¶ 21 (citing Ex. 19, Sybertz

1997 at 633) ("PDE5 inhibitors … also inhibit PDE6").[15] Thus, in July 1997 the skilled person would believe that what Lilly now calls a selective PDE5 inhibitor did not even exist, the patent would be construed to cover the use of zero of the illustrated examples, and it would be invalid for lack of written description.[16]

d. PDE11 had not yet been discovered. Ex. 1-B, Bell Validity Rpt. ¶ 68.

Lilly's construction is plain wrong, which is why it has also retreated to a backup plan – arguing the skilled person would have performed the fractionation test of the patent on prostate tissue and found PDE11, and since tadalafil is non-selective against PDE11 Lilly wins. Dkt. 174, Lilly Non-Infringement Br. at 8, 11 (¶ 6), 12, 13. Lilly's backup "prostate-based" claim construction is long on speculation and short on expert testimony. And again Lilly neglects to mention critical data that shows that even if Lilly were right about this "prostate-based" construction, it loses.

[15] Even though tadalafil was known in July 1997, its selectivity of PDE5 over PDE6 was not generally known, and had not been featured in Lilly's patents. *See* Ex. Ex. 19, Sybertz 1997 at 633) ("PDE5 inhibitors … also inhibit PDE6"); Ex. 20, US Patent No. 5,859,006 at col 48, ll. 28-29 (Lilly tadalafil patent reporting only that the compounds are "highly selective").

[16] Because the state of the art in July 1997 supports UroPep's position, Lilly attempts to shift focus to what a person of skill would have known at the time of the 2010 amendment. *See* Dkt. 174, Lilly Non-Infring. Br. 9-10. Lilly says this case is "similar," "in some regards," to *Motorola, Inc. v. Analog Devices, Inc.*, No. 1:03-cv-131, 2004 WL 5633739 (E.D. Tex. July 15, 2004), where the court considered the state of the art at the time of the amendment when construing the amended the claims. But the *Motorola* court acknowledged that Federal Circuit caselaw dictates that, when construing amended claims, "the date of the original application should be used." *Id.* at *2 (citing *Schering Corp. v. Amgen Inc.*, 222 F.3d 1347, 1352-54 (Fed. Cir. 2000)). And the very narrow circumstances that led the *Motorola* court to consider how certain terms would be understood at the time of amendment – i.e., that the amended claims would otherwise be broader than the scope of the original application, *id.*, – are not present here.

C. Lilly's Prostate-Based Construction Is Supported By No Evidence And Lilly Conceals That It Leads To A Finding Of Infringement Anyway

Lilly categorically asserts that, if one fractionates prostate tissue, PDE11 will be discovered in a separate fraction. Lilly Non-Infringement Br. at 8 ("performing the peak fractionation test on prostate tissue would let the researcher know that some PDE enzyme (known or unknown) was reactive in the prostate issue [sic]."). Lilly tells the Court that finding a PDE11 fraction from prostate tissue was "likely" four times. *Id.* at 11, 12, 13. But Lilly's expert Dr. Beavo did not say in his unsworn expert report that finding PDE11 was "likely."

> Therefore, although PDE11 had not been characterized in 1997, one *might* still be able to use a peak fraction method with prostatic tissue to determine an inhibitor's selectivity between various fractions, one of which would likely contain PDE11. The peak fraction assays, therefore, could have picked up PDE 11 activity *if abundant enough in that tissue*. The peak fractionation test *could potentially allow* an effect of an inhibitor to be evaluated on a fraction that contains PDE11 activity without actually knowing its identity.

Ex. 21, Beavo Resp. Rpt. ¶ 28 (emphases added). It is hard to imagine a more hedged and equivocal opinion. This speculation is accompanied by precisely zero evidence that anyone has ever found PDE11 through the fractionation of prostate or any other tissue. Tissue fractionation had been going on for quite some time before July 1997 and no one had discovered PDE11 (or any fraction that would later be identified as PDE11). Lilly's own expert could not bring himself to say that finding PDE11 this way was "likely," but Lilly exaggerates yet again.

UroPep has been consistent, and advanced a construction consistent with the specification (which refers to five sPDEs and provides examples of selective PDE5 inhibitors that also inhibit PDE6), the prosecution of the '061 patent, and the undisputed state of the art – where all PDE5 inhibitors were thought to also inhibit PDE6. But in fact UroPep could be forgiven for responding to Lilly's "prostate" construction with an eager agreement – because the use of

tadalafil to treat BPH would infringe under this construction. Lilly has decided not to tell the Court that its own data shows this is the case.

Lilly says that PDE11 would "likely" be found through fractionation of prostate tissue then points out that tadalafil is less than 20x selective for PDE5 over PDE11A1. Dr. Beavo, Lilly's expert, in his hedged and equivocal "might … if … could potentially" opinion did not say that PDE11A1 would be found. Why? Because Lilly has published that PDE11A1 is not found in the prostate, but rather PDE11A4, for which tadalafil has a 40x greater selectivity for PDE5. Yes, Lilly has published research that shows that everything they are saying in this briefing about the inevitable discovery of PDE11 in the prostate would just lead to a finding of infringement.

In 2005, Lilly ICOS employees, including Dr. Florio, published their paper on PDE11A "localization in human tissues." Ex. 22, Loughney et al. Notably, they did not fractionate human tissue looking for PDE11 peaks – they used PDE11A antibodies and recombinant PDE11A splice variants to discover whether PDE11 was in the prostate and other tissues. And what did Lilly discover? Contrary to prior researchers, using what Lilly said are superior analytical tools, "in prostate tissue, we detected only PDE11A4 protein." *Id.* at 323. Of course, as the article notes and Lilly's Cialis label says, and Lilly has to admit, "tadalafil … had a 40-fold selectivity for inhibition of PDE5A, compared to PDE11A4." *Id.* at 324.

To sum up, if the skilled person did the fractionation of prostate tissue test that Lilly thinks is now the touchstone of what the '124 patent is about, they "might … if … could potentially" get a PDE11 fraction. This fraction would, according to Lilly's research but not its brief, contain only PDE11A4, against which tadalafil is 40x less selective than it is against PDE5. UroPep reiterates that this entire PDE11 discussion is a sideshow, because PDE11 is irrelevant to the claim construction and the case. But should the Court entertain Lilly's prostate

proposal, then summary judgment of infringement in favor of UroPep should still be granted. Making arguments like these and relying on the adversary system to surface prior contradictory sworn testimony from its experts and Lilly's own published research is why the Court should also deny summary judgment of no willfulness.

III. THE COURT SHOULD DENY SUMMARY JUDGMENT OF NO WILLFULNESS

Lilly's infringement is willful because it has consistently offered non-infringement and invalidity arguments such as those discussed earlier in this brief. The jury should be allowed to determine whether Lilly's undisputed knowledge of the '124 patent, combined with the '124 patent's plain language, which clearly covers Cialis for BPH, and Lilly's desperate litigation tactics, proves that Lilly acted willfully.

In *Halo Electronics, Inc. v. Pulse Electronics, Inc.*, 136 S.Ct. 1923, 1933-34 (2016), the Supreme Court rejected "any rigid formula for awarding enhanced damages under § 284," and instructed courts "take into account the particular circumstances of each case in deciding" whether to enhance damages under § 284. *See also id.* at 1934 (eliminating the "clear and convincing" burden of proof that previously accompanied a willfulness claim). "Willfulness of behavior is a classical jury question of intent. When trial is had to a jury, the issue should be decided by the jury." *WBIP*, 829 F.3d at 1341.

Lilly was informed of the '124 patent, and the fact that it covers sales of Cialis for BPH, a few months after the patent issued. Ex. 23, Larsen Letter. The '124 patent's claims plainly cover using Cialis for treatment of BPH. Lilly needed no more information to fully understand the reasons that its activities infringed the '124 patent. Nonetheless, Lilly chose to ignore UroPep's overtures, and continued aggressively promoting the BPH indication to both doctors and

consumers. *See* Ex. 16, Cialis Label at 1, 2; Ex. 24, Sliwinski Rpt., ¶¶ 42-44; *Id.* at Ex. 7, Cialis Promotional Materials for Physicians; Ex. 25, Knobloch Decl., ¶¶ 3-4.

With UroPep's Complaint, Dkt. 1, Lilly received yet more detailed information regarding the basis for UroPep's infringement claims. And Lilly received UroPep's infringement contentions – which further spell out why Cialis is covered by the '124 patent – in late 2015.[17] Lilly thus knew why it infringed the '124 patent.

Lilly asserts that it has not willfully infringed the '124 patent because the parties "disagree as to the scope and validity of the '124 patent," and that "Lilly had, and still has, a good faith belief that there is no infringement." Dkt. 174, Lilly Br. at 16. But Lilly presents no evidence of its purported beliefs. Lilly has never asserted an opinion of counsel defense or produced any documents that could support such a defense, and the deadline for doing so has long passed. *See* Dkt. 117, Fourth Amended Docket Control Order, at 3 (setting a July 14, 2016 deadline for compliance with P.R. 3-7 (Opinion of Counsel Defenses)).[18]

In the absence of any direct evidence of Lilly's purported belief that it didn't infringe, Lilly seeks to avoid willfulness by stressing the objective reasonableness of its defenses to infringement. *See* Dkt. 174, Lilly Br. at 16. But an objectively reasonable defense to infringement does not preclude willful infringement; what matters is whether Lilly actually believed it did not infringe. *See Halo Electronics,* 136 S.Ct. at 1933 ("The subjective willfulness

[17] Lilly incorrectly asserts that "the sum total of UroPep's willfulness argument is that it notified Lilly of the '124 patent and Lilly continues its sales of Cialis." Dkt. 174, Lilly Br. at 15. In fact, UroPep's interrogatory responses identified numerous additional facts that support UroPep's willfulness claim, including UroPep's infringement contentions; UroPep's Complaint and exhibits; Lilly's acknowledgement of receiving UroPep's notice letter; and a long list of additional filings and exhibits in this case. See Ex. 26, UroPep Resp. to Lilly Interrogs. at 12-13. Lilly's recent litigation conduct further supports UroPep's willfulness claims.

[18] Subsequent docket control orders have not included this deadline, as they were all issued after the deadline passed.

of a patent infringer, intentional or knowing, may warrant enhanced damages, without regard to whether his infringement was objectively reckless."). That said, the objective reasonableness (or unreasonableness) of Lilly's defenses to infringement is still relevant to the determination of willfulness. *See WesternGeco L.L.C. v. ION Geophysical Corp.*, 837 F.3d 1358, 1363 (Fed. Cir. 2016) (objective reasonableness is one of the many factors courts may consider when determining willfulness). And an objective review of the defenses Lilly has asserted – and the desperate tactics it has used to promote those defenses – demonstrate Lilly's willfulness.

Lilly's conduct in the present round of summary judgment briefing is particularly telling. First, Lilly did not tell the Court that Dr. Florio's declaration directly contradicts Lilly's argument that UroPep cannot rely on the selectivity data in the label for Cialis to prove infringement because Lilly tested tadalafil using recombinant-sourced PDEs. *See* Dkt. 174, Lilly Noninfring. Br. 4, 13-14.

Second, in another attempt to conjure up a non-infringement argument, Lilly wrongly asserts that a peak fraction test conducted on prostatic tissue would "likely" show PDE11 "in a peak fraction," and that the results of such a test "would likely not support the required 20-fold selective threshold." Dkt. 174, Lilly Noninfring. Br. 13. As explained above, Lilly's arguments are not supported by its own experts' hedged opinions in an unsworn report. And, even more disconcerting, Lilly's arguments are directly contradicted by a paper published by Lilly employees showing that only one isozyme of PDE11 is present in the prostate – PDE11A4 – and that tadalafil is 40 times more selective for PDE5 than PDE11A4. *See* Ex. 22, Loughney at 323-24. Thus, in fact, a person of ordinary skill conducting a peak fraction test of tadalafil on prostate tissue would have to conclude that tadalafil infringes. But, like the earlier Florio declaration, Lilly withheld this paper from the Court.

Lilly's earlier round of summary judgment filings fare no better. Lilly first argued that "an inhibitor of phosophodiesterase (PDE) V" was a "means plus function" limitation and, because tadalafil is not expressly disclosed in the specification, Lilly did not infringe. Dkt. 119, Lilly Means Plus Function Br., at 1. But, as the Court noted in its decision denying Lilly's motion, Federal Circuit precedent establishes "that means-plus-function analysis is not applicable to the method claims at issue in this case." Dkt. 149, Mem. Op. & Order, at 8-9. Lilly also argued, in the alternative, that the '124 patent claims are invalid for failing to meet the written description requirement of § 112. Dkt. 120, Lilly Written Description Br., at 1. One of the key "facts" underlying Lilly's written description motion was that, in 1997, "the field of PDE inhibitors was emerging and unpredictable." *Id.* at 3. *See also id.* at 16-17. But, as the Court noted in its decision denying Lilly's motion, UroPep identified "evidence in the record that persons of skill in the art would have been aware of hundreds of PDE V inhibitors" at the time, including tadalafil. Dkt. 149, Mem. Op. and Order at 36. The jury should be allowed to determine whether Lilly's unsuccessful efforts to avoid liability support or detract from UroPep's willfulness claim.

CONCLUSION

For the foregoing reasons, Lilly's motions for summary judgment should be denied.

UROPEP'S RESPONSE TO LILLY'S STATEMENT OF UNDISPUTED FACTS IN SUPPORT OF LILLY'S MOTION FOR SUMMARY JUDGMENT OF INDEFINITENESS

UroPep responds to Lilly's Statement of Undisputed Material Facts Relating to Indefiniteness in corresponding numbered paragraphs:

1. Undisputed.

2. UroPep does not dispute that a compound's selectivity for one PDE can be measured against its selectivity for other PDEs by comparing the compound's IC_{50} values against different PDEs. However, as explained in Dr. Bell's report, while it was common at the time to "compare IC_{50} even across different tissue sources, to the extent that a person of skill in the art was looking for more robust selectivity data they would rely on data such as that in Takase 1993 and Seiki 1995 because those isoenzymes were not obtained from different species and tissue sources." Ex. 1-B, Bell Validity Rpt. ¶ 38.

3. Undisputed.

4. Undisputed.

5. Undisputed.

6. UroPep disputes that "different" fractionation methods and procedures were known in the art at the time. The fractionation described in the patent was a standard procedure that would have been well known to a person of skill in the art. Ex. 1-B, Bell Validity Rpt. ¶ 15.

7. UroPep does not dispute that different IC_{50} assays can produce different results, but UroPep disputes that such differences are material.

8. Undisputed.

9. Undisputed.

10. UroPep disputes Lilly's reliance on its expert reports, which are unsworn inadmissible hearsay. UroPep does not dispute that selectivity tests are subject to both measurement error and experimental error. However, as discussed in the argument section above, where greater precision was needed, a person of skill in the art could reduce both types of error using known methods, including methods discussed in the '124 patent.

11. Undisputed.

12. UroPep disputes Lilly's reliance on its expert reports, which are unsworn inadmissible hearsay. UroPep does not dispute that various experimental conditions could impact the results of a fractionation test. However, UroPep disputes the relevance of this fact, as a person of skill in the art looking for more robust selectivity data would know how to identify such data, and would be comfortable relying on such data to determine selectivity. *See* Ex. 1-B, Bell Validity Rpt. ¶¶ 15; 26; 28-30; 38.

13. Same response as ¶ 12.

14. Same response as ¶ 12.

15. UroPep generally agrees that test conditions can affect results, and that all scientific experiments are subject to possible measurement and/or experimentation errors. UroPep does not understand what Lilly means when it discusses what information is necessary in order "to infer relevance from IC_{50} values," and therefore disputes those statements. UroPep notes that a person of skill in the art would have no difficulty evaluating IC_{50} values to determine whether a given compound met the Court's selectivity requirement. *See* Ex. 1-B, Bell Validity Rpt. ¶ 15.

16. UroPep disputes Lilly's reliance on its expert reports, which are unsworn inadmissible hearsay. UroPep also disputes that the variations that may result from different test conditions would be important to a person of ordinary skill's ability to determine whether a compound met the patent's rule of thumb of 20x selectivity. Further, UroPep disputes that a person of ordinary skill would conduct the sorts of calculations that Lilly describes, because that person would not rely on high precision in IC_{50} measurements, but would rather look to the order of magnitude. *See* Ex. 1-B, Bell Validity Rpt. ¶¶ 15; 57.

17. Undisputed.

18. UroPep disputes the accuracy of Lilly's zaprinast table. As set-forth in the addendum to UroPep's Response Brief and explained in the argument section above, many of the articles that Lilly cites do not provide any measurement error, and are not intended to be used to calculate precise selectivity ratios. Further, Lilly's table misreports the selectivity ratios that are disclosed in some of the articles that Lilly cites.

19. UroPep disputes the accuracy of Lilly's zaprinast table. UroPep also disputes that a person of skill in the art would view these articles – many of which do not even report on measurement error – as carrying equal weight for someone trying to understand the selectivity of zaprinast. As Dr. Bell explains, when one accurately looks at the best studies, those that attempt to measure selectivity and control for what can be controlled, the variability that Lilly reports is reduced and zaprinast meets the Court's definition. Ex. 1-B, Bell Validity Rpt. ¶¶ 80-82.

20. UroPep does not dispute the first sentence of this paragraph. However, UroPep disputes that Daugan reports that zaprinast is 6.67 times more selective for PDE5 than for PDE1. Lilly miscalculates the selectivity ratio for zaprinast that is reported in the Daugan table that Lilly cites. In addition, Lilly ignores the measurement error reported in Daugan, which indicates that zaprinast could be as much as 21.7 times more selective for PDE5 than for PDE1. *See* Ex. 9, Daugan 2003 Part 1 at 4527-28.

21. UroPep disputes Lilly's reliance on its expert reports, which are unsworn inadmissible hearsay. UroPep also disputes that the '124 patent does not specify a specific fractionation method. First, fractionation was a well-known method for determining selectivity, and while test conditions might vary, the methodology outlined in the '124 patent was well-known. *See* Ex. 1-B, Bell Validity Rpt. ¶¶ 15, 30. Second, the '124 patent explicitly mentions one of the key ways to minimize experimental error – obtaining tissue from a single source. *See*

Ex. 7, '124 patent, col. 7, ll. 41-42; Ex. 1-B, Bell Validity Rpt. ¶ 38. UroPep does not dispute that the Galvan, Nicholson, and Truss papers describe tests using different tissue sources and species, but disputes Lilly's implication that these differences would have been relevant to a person of ordinary skill's understanding of the '124 patent's disclosure.

22. UroPep disputes Lilly's reliance on its expert reports, which are unsworn inadmissible hearsay. UroPep also disputes the relevance of this paragraph. As explained by Dr. Bell, "the '124 patent outlines the very standard procedure that would have been well known to a person of skill in the art." Ex. 1-B, Bell Validity Rpt. ¶ 30. And a person of skill in the art would not have difficulty using the '124 patent's rule of thumb of 20x selectivity to describe compounds as selective PDE5 inhibitors. *Id.* at ¶ 15. Further, as explained above, Lilly's own US Patent No. 6,451,807, defines selectivity by reference to IC_{50} ratios, and does not specify the experimental variables that Lilly lists in this paragraph.

UROPEP'S RESPONSE TO LILLY'S STATEMENT OF UNDISPUTED FACTS IN SUPPORT OF LILLY'S MOTION FOR SUMMARY JUDGMENT OF NON-INFRINGEMENT

UroPep responds to Lilly's Statement of Undisputed Material Facts Relating to "Inhibitor of Phosphodiesterase (PDE) V," in corresponding numbered paragraphs:

1. UroPep does not dispute that there are 11 PDE families (PDE1-PDE11). But UroPep disputes that each of these families contain multiple specific PDEs. Instead, they contain what UroPep's expert refer to as "splice variants." *See* Ex. 1-B, Bell Validity Rpt. ¶ 68. UroPep also disputes Lilly's reliance on its expert reports, which are unsworn inadmissible hearsay.

2. Undisputed.

3. UroPep does not dispute that the '124 patent discloses a peak fraction test for determining whether a substance is selective for a given specific PDE, and states that "a substance is considered an inhibitor of an sPDE if the" IC50 of the substance "is at least 20 times

lower in the respective peak fraction containing the specific phosphodiesterase than in other peak fractions." Ex. 7, col. 8, ll. 5-9. UroPep disputes the remaining statements in this paragraph, and notes that Lilly misquotes the cited portion of the patent, because the patent does not limit the relevant discussion to PDE5, and the word "all" does not appear before "other peak fractions."

4. UroPep does not dispute that it was expected in 1997 that additional PDEs would be discovered. However, UroPep disputes Lilly's reliance on its expert reports, which are unsworn inadmissible hearsay.

5. UroPep does not dispute that PDEs 1-11 were known by March 28, 2000. But UroPep disputes the relevance of this fact, as the '124 patent claims must be interpreted in light of the state of the art in July 1997, not March 2000.

6. UroPep disputes Lilly's reliance on its expert reports, which are unsworn inadmissible hearsay. UroPep does not dispute that PDE11A4 and PDE5 are present in the prostate. *See* Ex. 22, Loughney (2005) at 323. However, UroPep disputes that a person of ordinary skill administering a peak fraction test on prostatic tissue in 1997 would have likely seen PDE11 in a peak fraction. Further, tadalafil is more than 40-fold selective for PDE5 over PDE11A4, *see id.* at 324, so anyone testing tadalafil's selectivity for PDEs on prostatic tissue would have concluded that tadalafil is a highly selective PDE5 inhibitor.

7. UroPep agrees that Dr. Bell did not independently test tadalafil's selectivity for PDE5. Dr. Bell's infringement report cites Ex. 5, Daugan Part 2 2003, and the Cialis label, Ex. 16, and other sources as evidence of tadalafil's selectivity for PDE5. *See* Ex. 1-A, Bell Infring. Rpt. ¶¶ 16-19. Nor does UroPep dispute that these sources relied at least in part on recombinant PDEs, though Daugan also relied in part on testing bovine PDE. UroPep disputes the relevance of these facts, as the '124 patent does not require the use of any particular test; Lilly agrees that

tests using recombinant-source PDEs tend to be more accurate; and Lilly does not dispute that tadalafil is, in fact, significantly more than 20x selective for PDE5 over PDEs 1-4. UroPep does not dispute that tadalafil is 14-fold more potent for PDE5 than for PDE11A1. UroPep disputes the remaining statements in this paragraph, including the suggestion that the tests relied on in Daugan or the Cialis label are "different tests" than the selectivity tests described in the '124 patent and used in the art at the time.

UroPep does not dispute Lilly's Statement of Undisputed Material Facts Relating to Willfulness, except that UroPep disagrees that its notice letter did not explain how UroPep believed that Lilly is infringing the '124 patent. That letter explained that Lilly's sales of Cialis for prophylaxis or treatment of BPH required a license to the '124 patent. *See* Ex. 23, Larsen Letter. Lilly is a sophisticated drug manufacturer and the language of the '124 patent is clear. No further information was needed for Lilly to understand why the '124 patent covered Lilly's activities.

Addendum – Annotated Lilly Table On Zaprinast

Articles highlighted in orange report no measurement error

Reference	Publication Date	Tissue Type	PDE-5 $IC_{50}(\mu M)$	PDE-1 $IC_{50}(\mu M)$	Selectivity PDE-5/PDE-1
Torphy, et al., J. Pharm. Exp. Therap., 265(3):1213-1223	1993	Human trachealis	0.3	> 30	>100 fold
Truss, et al., Urology, 45(5):893-901	1995	Porcine bladders	4 ± 23%*	13 ± 16%	3.25 fold
Truss, et al., Urol Res, 24:123-128	1996	Human detrusor	700	1000 (c-AMP) 200 (c-GMP)	1.4 fold (or 0.29 fold)
Coste and Grondin, Biochem Pharmacol, 50(10):1577-1585	1995	PDE-1, 3, 5: Bovine aorta; PDE- 2 & 4: human recomb.	0.2 ± 50%	3 ± 20%	15 fold
Saeki, et al., J Pharm Exp. Therap., 272(2):825-831	1995	Porcine aorta	0.51 ± 20%	49.4 ± 5%	96.9 fold
Terrett et al., Bioorganic & Med Chem Letters, 6(15):1819-1824	1996	PDE-1: rate liver; PDE-3: rabbit platelets; PDE-5: rabbit platelets OR human corpus cavernosum	2	9.4	4.7 fold
Takase, et al., J. Med. Chem., 36:3765-3770	1993	Porcine aorta	0.45 ± 27%	32.2 ± 16%	71.5 fold
Daugan, et al., J. Med. Chem., 46:4525-4532	2003	PDE-1, 3, 5: Bovine aorta; PDE- 2 & 4: human recomb.	0.2 ± 25%	2.6 ± 25%	13 fold
Souness, et al., Br. J. Pharmacol., 98:725-734	1989	Rat aorta	0.83	15.3 (if use Km for cAMP) 13.9 (if use Km for cGMP)	18.4 fold (if use K 60 16 Km for cGMP
Torphy, et al., Mol Pharmacol, 37:206-214	1989	Canine trachea	0.1	27	270 fold
Shahid et al., Br. J. Pharmacol., 104:471-477	1991	Bovine trachea	0.25 ± 23%	15.8 ± 25%	63 fold
Ahn, et al., Advances in Second Messenger and Phosphoprotein Research, Vol. 25, 271-288	1992	Bovine aorta	0.54	4	7.4 fold
Ahn, et al.	1992	Bovine coronary artery	0.96	11	11.5 fold
Ahn, et al.	1992	Rabbit aorta	0.5	10	20 fold
Ahn, et al.	1992	Rat aorta	1.5	5	3.33 fold

Notes

*One of three PDE5 fractions – no data presented on other two PDE5 fractions

Souness says 60-fold, Lilly has no disclosure of how it got its numbers

Lilly has no disclosure of how these numbers are calculated from the article – error rates extrapolated

Ahn reports error for PDE1 (± 10%) but PDE5 is based on a single measurement

Date: January 31, 2017

Respectfully submitted,

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CERTIFICATE OF SERVICE

The undersigned certifies that the foregoing document was filed electronically in compliance with Local Rule CV-5(a) on January 31, 2017. As such, this document was served on all counsel who are deemed to have consented to electronic service. Local Rule CV-5(a)(3)(A).

Date: January 31, 2017

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